Taiwanese Journal of Obstetrics & Gynecology 56 (2017) 432–436

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Review Article

Dyspnea in pregnancy

Shih-Yi Lee [a, d, g, h], Ding-Kuo Chien [b, c, d, e, f, g], Chien-Hsuan Huang [i], Shou-Chuan Shih [d, g, h], Wei-Cheng Lee [d, g, 1], Wen-Han Chang [b, c, d, e, f, g, *]

[a] Division of Pulmonary and Critical Care Medicine, Mackay Memorial Hospital, Taiwan
[b] Department of Emergency Medicine, Mackay Memorial Hospital, Taiwan
[c] Institute of Mechatronic Engineering, National Taipei University of Technology, Taiwan
[d] Department of Nursing, Mackay Junior College of Medicine, Nursing, and Management, Taipei, Taiwan
[e] Graduate Institute of Injury Prevention and Control, Taipei Medical University, Taipei, Taiwan
[f] School of Medicine, Taipei Medical University, Taipei, Taiwan
[g] Department of Medicine, Mackay Medical College, Taipei, Taiwan
[h] Department of Internal Medicine, Mackay Memorial Hospital, Taiwan
[i] Department of Rehabilitation, Tai-En Memorial Hospital, Taiwan

ARTICLE INFO

Article history:
Accepted 20 April 2017

Keywords:
Ventilation
Respiration
Pulmonary function test

ABSTRACT

Dyspnea in pregnancy is common. It can result from adaption to body changes in pregnancy and also from complications therein. Understanding the mechanisms of change in the respiratory system during pregnancy helps with the differential diagnosis of dyspnea in normal pregnancy as opposed to pathological dyspnea.

Introduction

Dyspnea in pregnancy is common [1–5]. Physiological changes during pregnancy influence maternal respiratory function and gas exchange, and may cause dyspnea in normal pregnancy. On the other hand, dyspnea can be caused by pregnancy complications, thus requiring optimal medical treatment. Making a correct assessment requires an understanding of the cardiopulmonary changes that occur during normal pregnancy, so as to recognize the syndrome of dyspnea. In this review, the aim was to outline the mechanisms of change within the respiratory system during pregnancy, and thus to enable a differential diagnosis of dyspnea in normal pregnancy as opposed to pathological dyspnea.

Material and methods

A focused literature search with consultation from a professional librarian was performed on data from January 1966 to December 2016. References of identified studies were also checked for relevancy. Hand-searches of relevant journals were also performed.

Respiratory system changes in pregnancy

Pregnancy induces profound changes in the mother, resulting in significant alterations to the normal physiology. Anatomical and respiratory physiological changes affect the respiratory system during pregnancy [6–9].

Alterations to pulmonary physiology during pregnancy

Pulmonary function changes in pregnancy

The volume in the lung, as total lung capacity, can be divided into tidal volume, inspiratory reserve volume, expiratory reserve volume, and residual volume. The net result of anatomical changes to the thoracic cage during pregnancy is a more barrel-chested appearance. The enlarging uterus moves the resting position of the diaphragm cephalad, and decreases the expiratory reserve volume (an approximate 10–20% reduction), as well as functional residual capacity [8,10–13].

However, the enlarged uterus does not limit the movement of the thoracic cage, but results in a 4.0 cm maximal increase in the level of the diaphragm, together with a 2.1 cm maximal increase

* Corresponding author. Department of Emergency Medicine, Mackay Memorial Hospital, No. 92, Sec. 2, Zhongshan N. Rd., Taipei City, 10449, Taiwan.
E-mail address: branden888@gmail.com (W.-H. Chang).
[1] Co-first author.

http://dx.doi.org/10.1016/j.tjog.2017.04.035

in the transverse diameter of the chest [4,13,14]. The subcostal angle increases progressively from an average of 68.5° in early pregnancy to 103.5° in late pregnancy, which remains the maximal inspiratory and expiratory pressure, and compensates for the reduction in abdominal replacement. Vital capacity (the volume combination with tidal volume, inspiratory reserve volume and expiratory reserve volume), the maximal amount of air that can be exhaled following maximal inspiration therefore remains constant or slightly increases during pregnancy [4,8,12,13,15].

Hormonal changes in pregnancy affect the upper respiratory tract and airway mucosa. The increase in estrogen during pregnancy causes airway mucosal hyperemia, edema and hypersecretion, and friability [16–18]; however, the patency of the airway and the ability of the gas exchange across the alveoli remain stable. The forced vital capacity, forced expiratory volume in 1 s, and the ratio of forced expiratory volume in 1 s to forced vital capacity tested by spirometer standing for the patency of the airway are similar in pregnancy and postpartum [5,8,19–21]. The differences of gas change of pulmonary respiration measured by the diffusing capacity of the lung for the monoxide are not significant between normal pregnant and non-pregnant women [22].

Taken together, although anatomical changes in pregnancy decrease the expiratory reserve volume and functional residual capacity, the vital capacity, airway patency, and gas exchange in healthy pregnant women are maintained (Table 1).

Ventilation changes in pregnancy

Minute ventilation and oxygen consumption increase over time in pregnancy [1,12,13,23,24]. The former increases significantly, beginning in the first trimester, and escalating to 20–40% above baseline at term [1,5,23,24]. Tidal volume increases by 30–35% and alveolar ventilation by 50–70%, with partial pressure of oxygen in arterial blood (PaO_2) ranging from 100 to 110 mmHg [12,24–26]. Oxygen consumption increases at the beginning of the first trimester, and by 20–33% per term, because of fetal demands and increased maternal metabolic processes [12]. In addition, physiological hyperventilation results in respiratory alkalosis, with the compensatory renal excretion of bicarbonate. Partial pressure of carbon dioxide in arterial blood ($PaCO_2$) reaches a plasma level of 28–32 mmHg, and bicarbonate decreases to 18–21 mmol/L. An arterial pH is maintained in the range of 7.40–7.47 [5,12,25–28].

Table 1
Modifications of pulmonary function in pregnancy.

	Changes
Spirometry	
FVC	← →
FEV1	← →
FEV1/FVC	← →
Lung volume	
TLC	← →
VC	← → ↑
TV	↑
ERV	↓
FRC	↓
Lung diffusion test	
D_LCO	← →

D_LCO: diffusing capacity of the lung for carbon monoxide; ERV: expiratory reserve volume; FEV1: forced expiratory volume in 1 s; FEV1/FVC: ratio of forced expiratory volume in 1 s to forced vital capacity; FRC: functional residual capacity; FVC: forced vital capacity; VC: vital capacity; TLC: total lung capacity; TV: tidal volume.

Multiple factors control breath (Fig. 1). The respiratory loop consists of a forward part (pulmonary respiration to maintain appropriate PaO_2 and $PaCO_2$), and a feedback part (chemoreceptors initiate pulmonary ventilation as the response to the PaO_2, PCO_2 and the concentration of hydrogen ions in the blood) [29–32]. Hyperventilation in human pregnancy has been shown to result from an increase in wakefulness drive to breathe [33,34], and an increase in the response to the chemoreceptor stimuli, including the increases in central and peripheral chemoreceptor sensitivity [12,34–36] and a reduction in the ventilator recruitment threshold [29,37–39], together with an increase in metabolism (the elevation of CO_2 production) [24]. In addition, when chemoreceptors response to the stimuli, tidal volume increases before the change in respiratory frequency [32]. Hyperventilation in pregnancy usually shows a higher tidal volume rather than a tachypnea [8,13,14].

The progressive increase in progesterone and estrogen during pregnancy is one of the factors that account for an increase in physical demands and hyperventilation [6,13,40]. Progesterone acts as a trigger of the primary respiratory center by reducing the threshold and by increasing the sensitivity of the respiratory center to CO_2 [35,36,41,42], while estrogen increases the number and sensitivity of progesterone receptors within the hypothalamus and medulla (the central neuronal respiratory-related areas) [42,43]. In addition, progesterone and estrogen increase the sensitivity of the peripheral chemoreceptor to hypoxic conditions [36]. Taken together, the elevation in progesterone and estrogen cause an increase in the wakefulness drive and central and peripheral chemoreceptor sensitivity, and a reduction in the ventilator recruitment threshold, resulting in hyperventilation in pregnancy (Fig. 2).

Dyspnea in normal pregnancy

Dyspnea occurs in normal pregnancy [5]. Milne et al. studied the incidence of dyspnea in 62 normal pregnant women [2]. Nine were aware of dyspnea during the first trimester, 31 by week 19, and 46 by week 31. Since dyspnea commences in the first gestation trimester, it is likely that biochemical and mechanical changes co-contribute to dyspnea during pregnancy. Additionally, the increase in respiratory drive in pregnancy has led to an increase in tidal volume rather than the respiratory frequency [8,13,14,24], reflecting that the dyspnea is not associated with tachypnea.

Dyspnea is awareness of respiratory distress or breathlessness [44,45]. The perception of breathlessness correlates well with respiratory drive [23,46,47]. Thus, an increase in respiratory drive in pregnancy can contribute to the perception of dyspnea [36,44,48]. Garcia-Rio et al. showed that normal pregnant women with dyspnea had a higher respiratory drive when responding to serum CO_2 and hypoxia, even though they had similar oxygen consumption, lung volume distribution and respiratory muscle strength to those with normal breathing [23].

Dyspnea is believed to be caused by a discrepancy or mismatch between the feed-forward message to the ventilatory muscles and the feedback from receptors monitoring the response of the ventilatory pump [45,49]. When the discrepancy is high, the dyspnea occurs [45,49]. The unfamiliar low level of $PaCO_2$ resulting from hyperventilation may contribute to women who are prone to developing dyspnea in pregnancy [50]. However, the other scientists believe that the excessive ventilation response to PaO_2 or $PaCO_2$ is related to the physiologic dyspnea in pregnancy [23,34,36]. Nevertheless, not only the increased respiratory drive because of

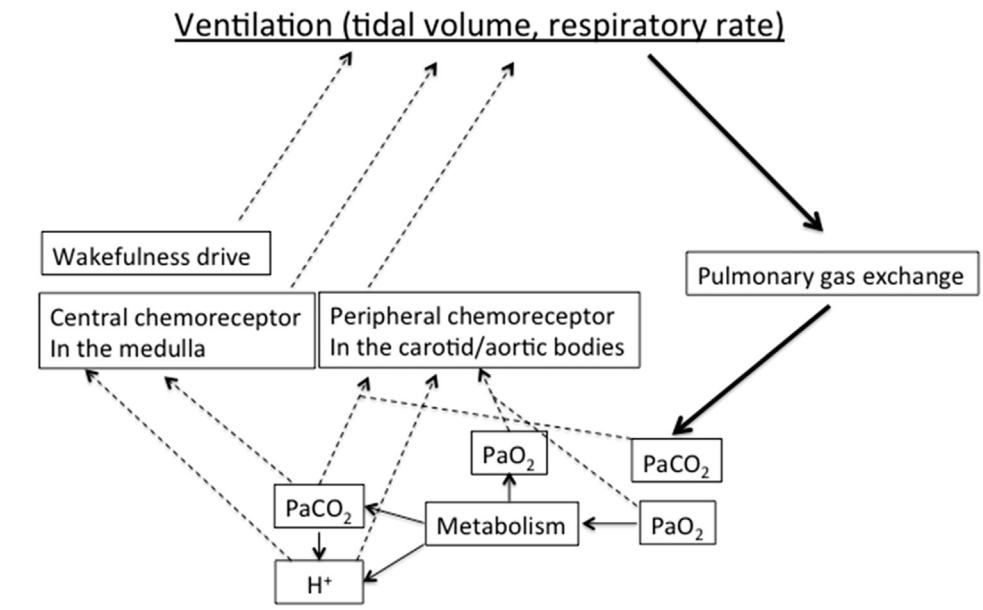

Fig. 1. Respiratory loop controls the pulmonary ventilation to maintain appropriate arterial oxygen and carbon dioxide tensions.

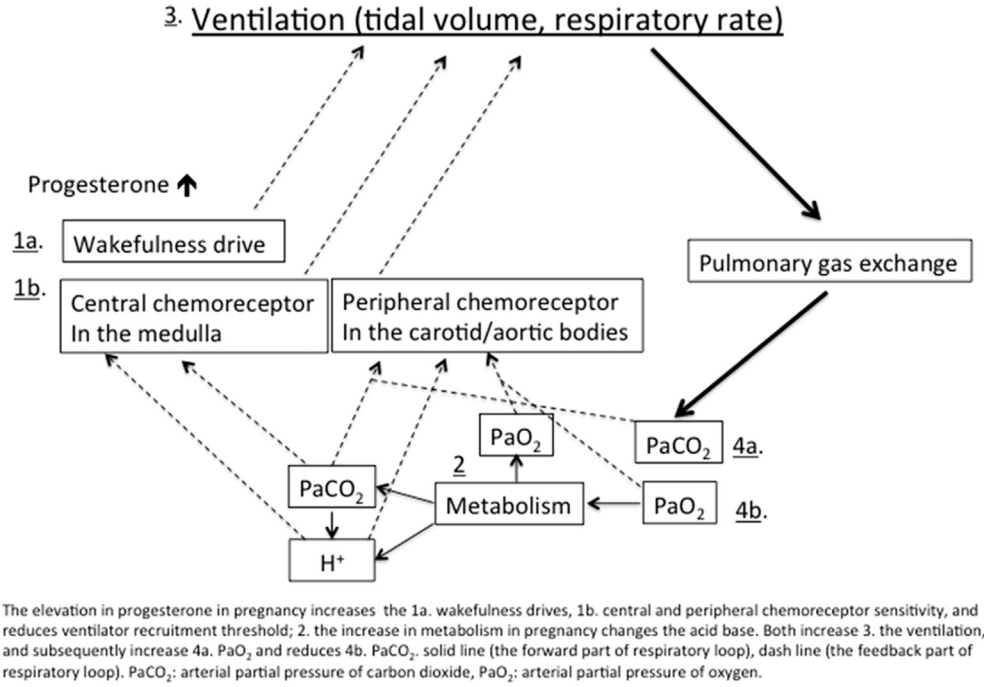

Fig. 2. Progesterone resets respiratory drive and leads to hyperventilation in pregnancy.

progesterone and estrogen elevation is responsible for hyperventilation and dyspnea in pregnancy [40,42], but the rise in the metabolism also counts. The complex interaction between respiratory drive and metabolism may have masked the statistical relationship among an increase in female sex hormone concentration, an increase in the respiratory drive, and the severity of the dyspnea during normal pregnancy in the studies [23,24].

In conclusion, dyspnea is common in pregnancy. The severity thereof relates to the sex hormone-related hyperventilation and pregnant-inducing metabolism elevation. Since airway patency, tidal volume and gas exchange are not limited in normal pregnancy, a careful history, chest X-ray, pulmonary function test and arterial gas evaluation are warranted to exclude pathological dyspnea in pregnancy (Table 2).

Table 2
Differential diagnosis of dyspnea in pregnancy.

Disease	History	Pulmonary function	Laboratory
Dyspnea in normal pregnancy	No associated wheeze or cough	Normal forced vital capacity, forced expiratory volume in 1st second, flow-volume loop, total lung capacity, vital capacity and D_LCO	Normal PaO_2 and arterial pH value
Asthma	Past history of recurrent cough/dyspnea/nocturnal dyspnea/wheezing	Positive response to provocation test or bronchodilator test	Hypoxic or hypercapnic respiratory failure in severe cases
Mechanical obstruction (larynx, trachea, main bronchi)	History of injury, aspiration, hemoptysis/wheezing over the trachea	Flattening of the Inspiratory or expiratory part of flow-volume loop/no response to bronchodilators	Diagnostic endoscopy
Pulmonary edema	Nocturnal dyspnea/wheezing/cardiomegaly/gallop rhythm/valvular disease/tocolytic therapy	Decreased forced vital capacity	Chest X-ray: cardiomegaly, interstitial edema, perihilar consolidation/echocardiography: mitral or aortic valve disease, left ventricular dilation or hypertrophy, hypocontractile left ventricle in peripartum, cardiomyopathy
Pulmonary embolism	Sudden onset of dyspnea/wheezing	Impaired D_LCO	Arterial hypoxemia/abnormal perfusion on ventilation
Amniotic fluid embolism	Acute respiratory distress during labor or delivery/cyanosis, shock, bleeding/wheezing	Impaired D_LCO	Disseminated intravascular coagulation/demonstration of fetal elements in the maternal circulation

D_LCO: the diffusing capacity of the lungs for carbon monoxide; PaO_2: partial pressure of oxygen in arterial blood.

Conflicts of interest

None.

References

[1] Tenholder MF, South-Paul JE. Dyspnea in pregnancy. Chest 1989;96:381–8.
[2] Milne JA, Howie AD, Pack AI. Dyspnoea during normal pregnancy. Br J Obstet Gynaecol 1978;85:260–3.
[3] Gilbert R, Auchincloss Jr JH. Dyspnea of pregnancy. Clinical and physiological observations. Am J Med Sci 1966;252:270–6.
[4] Thomson KJ, Cohen ME. Studies on the circulation in pregnancy: II. Vital capacity observations in normal pregnant women. Surg Gynecol Obstet 1938;66:591–603.
[5] Milne JA. The respiratory response to pregnancy. Postgrad Med J 1979;55:318–24.
[6] LoMauro A, Aliverti A. Respiratory physiology of pregnancy: physiology masterclass. Breathe 2015;11:297–301.
[7] Fishburne JI. Physiology and disease of the respiratory system in pregnancy. A review. J Reprod Med 1979;22:177–89.
[8] Weinberger SE, Weiss ST, Cohen WR, Weiss JW, Johnson TS. Pregnancy and the lung. Am Rev Respir Dis 1980;121:559–81.
[9] Lapinsky SE, Kruczynski K, Slutsky AS. Critical care in the pregnant patient. Am J Respir Crit Care Med 1995;152:427–55.
[10] Bonica JJ. Maternal respiratory changes during pregnancy and parturition. Clin Anesth 1974;10:1–19.
[11] Cugell DW, Frank NR, Gaensler EA, Badger TL. Pulmonary function in pregnancy. I. Serial observations in normal women. Am Rev Tuberc 1953;67:568–97.
[12] Prowse CM, Gaensler EA. Respiratory and acid-base changes during pregnancy. Anesthesiology 1965;26:381–92.
[13] Contreras G, Gutierrez M, Beroiza T, Fantin A, Oddo H, Villarroel L, et al. Ventilatory drive and respiratory muscle function in pregnancy. Am Rev Respir Dis 1991;144:837–41.
[14] Gilroy RJ, Mangura BT, Lavietes MH. Rib cage and abdominal volume displacements during breathing in pregnancy. Am Rev Respir Dis 1988;137:668–72.
[15] Turner AF. The chest radiograph in pregnancy. Clin Obstet Gynecol 1975;18:65–74.
[16] Toppozada H, Michaels L, Toppozada M, El-Ghazzawi I, Talaat M, Elwany S. The human respiratory nasal mucosa in pregnancy. An electron microscopic and histochemical study. J Laryngol Otol 1982;96:613–26.
[17] Koehler KF, Helguero LA, Haldosen LA, Warner M, Gustafsson JA. Reflections on the discovery and significance of estrogen receptor beta. Endocr Rev 2005;26:465–78.
[18] Audie JP, Janin A, Porchet N, Copin MC, Gosselin B, Aubert JP. Expression of human mucin genes in respiratory, digestive, and reproductive tracts ascertained by in situ hybridization. J Histochem Cytochem Offic J Histochem Soc 1993;41:1479–85.
[19] McAuliffe F, Kametas N, Costello J, Rafferty GF, Greenough A, Nicolaides K. Respiratory function in singleton and twin pregnancy. BJOG Int J Obstet Gynaecol 2002;109:765–9.
[20] Milne JA, Mills RJ, Howie AD, Pack AI. Large airways function during normal pregnancy. Br J Obstet Gynaecol 1977;84:448–51.
[21] Kolarzyk E, Szot WM, Lyszczarz J. Lung function and breathing regulation parameters during pregnancy. Archives Gynecol Obstet 2005;272:53–8.
[22] Gazioglu K, Kaltreider NL, Rosen M, Yu PN. Pulmonary function during pregnancy in normal women and in patients with cardiopulmonary disease. Thorax 1970;25:445–50.
[23] Garcia-Rio F, Pino JM, Gomez L, Alvarez-Sala R, Villasante C, Villamor J. Regulation of breathing and perception of dyspnea in healthy pregnant women. Chest 1996;110:446–53.
[24] Jensen D, Duffin J, Lam YM, Webb KA, Simpson JA, Davies GA, et al. Physiological mechanisms of hyperventilation during human pregnancy. Respir Physiol Neurobiol 2008;161:76–86.
[25] Liberatore SM, Pistelli R, Patalano F, Moneta E, Incalzi RA, Ciappi G. Respiratory function during pregnancy. Respir Int Rev Thorac Dis 1984;46:145–50.
[26] Pernoll ML, Metcalfe J, Kovach PA, Wachtel R, Dunham MJ. Ventilation during rest and exercise in pregnancy and postpartum. Respir Physiol 1975;25:295–310.
[27] Wolfe LA, Kemp JG, Heenan AP, Preston RJ, Ohtake PJ. Acid–base regulation and control of ventilation in human pregnancy. Can J Physiol Pharmacol 1998;76:815–27.
[28] Lim VS, Katz AI, Lindheimer MD. Acid–base regulation in pregnancy. Am J Physiol 1976;231:1764–9.
[29] Duffin J. Role of acid–base balance in the chemoreflex control of breathing. J Appl Physiol 2005;99:2255–65.
[30] Lahiri S, Forster 2nd RE. CO_2/H(+) sensing: peripheral and central chemoreception. Int J Biochem Cell Biol 2003;35:1413–35.
[31] Duffin J, McAvoy GV. The peripheral-chemoreceptor threshold to carbon dioxide in man. J Physiol 1988;406:15–26.
[32] Duffin J, Mohan RM, Vasiliou P, Stephenson R, Mahamed S. A model of the chemoreflex control of breathing in humans: model parameters measurement. Respir Physiol 2000;120:13–26.
[33] Jensen D, Wolfe LA, Slatkovska L, Webb KA, Davies GA, O'Donnell DE. Effects of human pregnancy on the ventilatory chemoreflex response to carbon dioxide. Am J Physiol Regul Integr Comp Physiol 2005;288:R1369–75.
[34] Jensen D, Webb KA, O'Donnell DE. The increased ventilatory response to exercise in pregnancy reflects alterations in the respiratory control systems ventilatory recruitment threshold for CO_2. Respir Physiol Neurobiol 2010;171:75–82.
[35] Lyons HA, Antonio R. The sensitivity of the respiratory center in pregnancy and after the administration of progesterone. Trans Assoc Am Phys 1959;72:173–80.
[36] Moore LG, McCullough RE, Weil JV. Increased HVR in pregnancy: relationship to hormonal and metabolic changes. J Appl Physiol 1987;62:158–63.
[37] Hirabayashi Y, Shimizu R, Saitoh K, Fukuda H, Igarashi T. Acid-base state of cerebrospinal fluid during pregnancy and its effect on spread of spinal anaesthesia. Br J Anaesth 1996;77:352–5.
[38] Stewart PA. Modern quantitative acid-base chemistry. Can J Physiol Pharmacol 1983;61:1444–61.
[39] Lindinger MI, Heigenhauser GJ. Effects of gas exchange on acid-base balance. Compr Physiol 2012;2:2203–54.
[40] Behan M, Wenninger JM. Sex steroidal hormones and respiratory control. Respir Physiol Neurobiol 2008;164:213–21.
[41] Slatkovska L, Jensen D, Davies GA, Wolfe LA. Phasic menstrual cycle effects on the control of breathing in healthy women. Respir Physiol Neurobiol 2006;154:379–88.

[42] Bayliss DA, Millhorn DE. Central neural mechanisms of progesterone action: application to the respiratory system. J Appl Physiol 1992;73:393–404.
[43] Hosenpud JD, Hart MV, Morton MJ, Hohimer AR, Resko JA. Progesterone-induced hyperventilation in the Guinea pig. Respir Physiol 1983;52:259–64.
[44] Campbell EJ, Howell JB. The sensation of breathlessness. Br Med Bull 1963;19:36–40.
[45] Dyspnea. Mechanisms, assessment, and management: a consensus statement. American Thoracic Society. Am J Respir Crit Care Med 1999;159:321–40.
[46] Kikuchi Y, Okabe S, Tamura G, Hida W, Homma M, Shirato K, et al. Chemosensitivity and perception of dyspnea in patients with a history of near-fatal asthma. N Engl J Med 1994;330:1329–34.
[47] Wood JB, Frankland AW, Eastcott HH. Bilateral removal of carotid bodies for asthma. Thorax 1965;20:570–3.
[48] Hannhart B, Pickett CK, Weil JV, Moore LG. Influence of pregnancy on ventilatory and carotid body neural output responsiveness to hypoxia in cats. J Appl Physiol 1989;67:797–803.
[49] Parshall MB, Schwartzstein RM, Adams L, Banzett RB, Manning HL, Bourbeau J, et al. An official American Thoracic Society statement: update on the mechanisms, assessment, and management of dyspnea. Am J Respir Crit Care Med 2012;185:435–52.
[50] Gilbert R, Epifano L, Auchincloss Jr JH. Dyspnea of pregnancy. A syndrome of altered respiratory control. Jama 1962;182:1073–7.